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Thrombotic Thrombocytopenic Purpura: Early and Late Responders

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Thrombotic thrombocytopenic purpura (TTP) is characterized by micro-angiopathic hemolytic anemia (MAHA), thrombocytopenia, neurological symptoms, renal involvement, and fever. We describe our experience in 70 serially encountered TTP patients in the last decade who were treated with a standard therapeutic plasma exchange (TPE) protocol. Seventy percent of the patients were females. The median age of the patients was 43 years (range: 8–80). Sixty patients (85.7%) had a complete response to TPE therapy. This represented 91% of 66 who received at least one TPE. Ten patients died, two patients died before and two during the first plasma exchange. The median number of TPEs performed was nine (range: 1–85). Thirty-five (58%) out of 60 responded to 3–9 TPEs, and 25 (42%) required 10–34 TPEs for the response. The median total plasma volume exchanged was 28 liters (range: 2.7–250 L) and the mean plasma volumes exchanged during each prodcedure was 3.2 (SD ± 1.09 L). The patients were classified into early responders (ER) and late responders (LR). ERs had a mean platelet count of 180 × 10^9/L by Day 5, mean LDH of 643 IU/L by Day 7, and required median of seven TPEs. LRs had a mean platelet count of 122 × 10^9/L by Day 5, mean LDH of 885 IU/L by Day 7, and required median of 19 TPEs (P = 0.001). The platelet counts were significantly higher (P = 0.01–0.03) in ERs on Days 1, 3, and 5 as compared to LRs but the LDH did not differ significantly. Seventy-seven percent of LRs had exacerbation of TTP and 18% had relapse as compared to 7% each in ERs. Thirteen patients were in coma/semicoma at presentation. Out of these, six died, making coma a bad prognostic indicator. Five of the seven survivors in coma had received two single-plasma volume exchanges on Day 1. In conclusion, 91% of TTP patients had an excellent response to plasma exchange therapy with FFP. Coma/semicoma appears to be a bad prognostic indicator. LRs needed prolonged treatment with a greater number of patients experiencing exacerbation and relapse of TTP as compared to ERs. Am. J. Hematol. 54:102–107, 1997 © 1997 Wiley-Liss, Inc.

Key words: thrombotic thrombocytopenic purpura; thrombocytopenia; microangiopathic hemolytic anemia; plasma exchange; coma

INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is classically characterized by a pentad of consumptive thrombocytopenia, microangiopathic hemolytic anemia (MAHA), neurological involvement, renal abnormalities, and fever. This syndrome was progressive and invariably fatal before the introduction of plasma exchange therapy [1]. Since then, the mortality has been significantly reduced [2–4]. The etiology of primary (idiopathic) TTP is unclear while a secondary form of the syndrome appears to be associated with underlying conditions such as autoimmune disorders, certain drugs, pregnancy, cancer, and bone marrow transplantation [5–9]. Generalized endothelial cell damage in the microcirculation with resultant platelet-thrombi formation appears to be the common pathogenic mechanism for primary and secondary forms of TTP [10]. The clinical and laboratory abnormalities in TTP patients are often completely reversed with plasma therapy. However, there is a subset of TTP patients who are either resistant to plasma therapy or have a remitting and relapsing course and these patients have been successfully managed with vincristine or splenectomy [11–13].

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Only one large single center study of serially encountered patients with TTP has been reported previously [14]. Over the past decade, we encountered and provided primary treatment to 70 patients with TTP. This experience has provided an unusual opportunity to characterize the clinical course and outcome in a large number of serially encountered patients treated with a standard plasma exchange regimen.

PATIENTS AND METHODS

This study is a retrospective analysis of primary TTP patients treated between January 1985 and June 1995 in 28 hospitals serviced by The Blood Center of Southeastern Wisconsin, Milwaukee, Wisconsin. The diagnosis of TTP was made when the patient presented with MAHA (anemia, presence of schistocytes in peripheral blood smear, and increased LDH), thrombocytopenia (platelet count $<100 \times 10^9$/L), neurological symptoms, and/or renal involvement. TTP was differentiated from hemolytic uremic syndrome (HUS) based on the presence of predominant neurological symptoms, MAHA, moderate to severe thrombocytopenia, and less severe involvement of the renal function. None of these TTP patients had renal involvement in the absence of neurological symptoms.

Treatment Plan

An initial consult occurred between the treating physician and the Blood Center physician and a general plan of management was decided. The first therapeutic plasma exchange (TPE) was usually performed within 4–6 hr of the request from the treating physician. The standard treatment protocol consisted of one plasma volume exchange with fresh frozen plasma (FFP) daily. Plasma volumes were calculated for each patient using the patient's body surface area (calculated using height and weight), sex, and hematocrit. However, depending upon the severity of the disease, either a 1.5 to 2.0 plasma volume exchange or one volume plasma exchange twice on Day 1 followed by daily one plasma volume exchange was performed in some cases. Most procedures were performed on Cobe Spectra Apheresis machines and some on IBM 2997 machines (Lakewood, CO). Adjunct therapy consisted of corticosteroids, anti-platelet drugs (aspirin and/or dipyridamole) and vincristine (VCR) in some cases. During the treatment period the patient's progress was assessed based on clinical and laboratory parameters (platelet count, hematocrit, LDH, peripheral blood smear for schistocytes, and serum creatinine).

Daily plasma exchanges were continued until clinical symptoms had disappeared and the platelet count and LDH had normalized. The majority of the patients received at least two additional plasma exchanges after the platelet count and LDH were normalized. For those TTP patients who had a late response or had exacerbation of the disease during the treatment period, the frequency of plasma exchange was gradually tapered from daily to alternate day and then twice a week before discontinuing.

Red cell transfusions were given for severe symptomatic anemia (Hb $\leq$ 8.0 gm/dl). Platelet transfusions were contraindicated after the diagnosis of TTP was established.

Criteria for Response

Complete response is defined as the disappearance of all clinical symptoms and normalization of the platelet count and serum LDH. *Partial response* is defined as some improvement in CNS symptoms and/or increase in platelet count by 50% and decrease in LDH by 50% as compared to the baseline values after seven TPEs. *No response* is defined as no improvement at all in clinical symptoms and laboratory values or the patient died. *Relapse* is arbitrarily defined as when a patient with a complete response returns after at least 2 weeks following the last plasma exchange with abnormal laboratory values and/or clinical symptoms. *Exacerbation* is defined as when the platelet count drops or the LDH increases after initial improvement during the treatment period or within 2 weeks from the last TPE.

Some patients were given diphenhydramine and acetaminophen prior to each TPE as a part of a particular hospital's transfusion policy, otherwise patients were premedicated only if they demonstrated allergic reactions to fresh frozen plasma.

Statistical analysis was done by applying *t*-test, Mann-Whitney U-test, and Chi-square test.

RESULTS

Clinical Features

Of the seventy TTP patients, 70% were females and 30% males, with an age range of 8–80 years (mean 47 years, median 43 years, Fig. 1). There were 14 cases below the age of 30 years, 40 cases between 30 and 60 years, and 16 cases over the age of 61 years. The clinical features at presentation are given in Tables I and II.

Response to Plasma Exchange

Sixty patients out of 70 (85.7%) had a complete response. Two patients died before starting TPE, and two died during the initial TPE. Of the 66 patients who received at least one complete TPE, there was a 91% complete response rate. Clinical symptoms generally disappeared within 24–72 hr after starting TPE and always before the hematological response occurred. The median number of plasma exchanges performed was nine (mean 13, range 1–85). The median total plasma volume exchanged was 28 liters (range: 2.5–250 L) and the mean plasma volume exchanged during each procedure was 3.28 liters (SD $\pm$ 1.09). Thirty-five out of 60 (58%) pa-

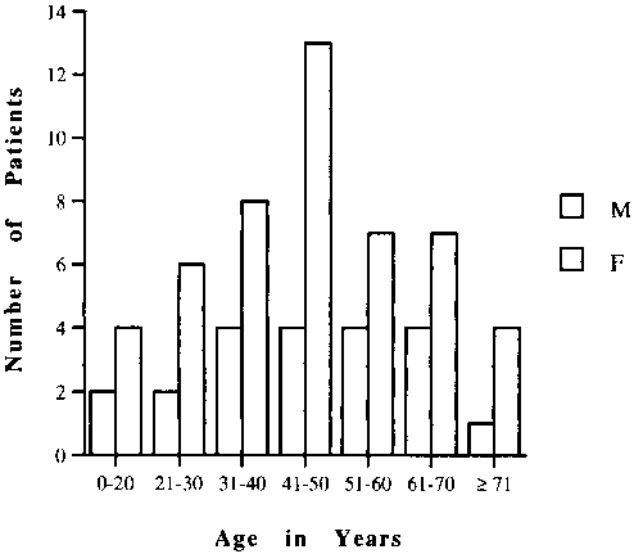

Fig. 1. Age and sex distribution in TTP patients.

TABLE I. Clinical Features at Presentation*

	N	%
MAHA	70	100
Thrombocytopenia	70	100
Neurological symptoms	60	86
Renal involvement	38	54
Fever	17	24
Classical pentad	10	14

*MAHA = microangiopathic hemolytic anemia.

TABLE II. Neurological Symptoms at Presentation

Symptoms	n (%)	Died (%)
Coma	13 (19)	6 (46)
Confusion, abnormal psyche	39 (56)	2 (5)
Paresis	15 (21)	0 (0)
Seizures	12 (17)	1 (8)
Headaches, visual distrubances	12 (17)	0 (0)

tients responded to therapy with normalization of platelet count and LDH after 3–9 plasma exchanges. The remaining 25 (42%) required 10–34 plasma exchanges to obtain the hematological response.

Relapse

Eleven patients out of the 60 (18%) who had a complete response, had a relapse of the disease from 45 days to 5 years after the last TPE. Six patients had one relapse, two had two, one had three relapses, and two patients had six relapses. All relapsed patients responded to repeat plasma exchange. One relapsed patient presented in a coma and died before plasma exchange could be started. Three relapsed patients also received VCR at a dose of 2 mg/wk for 2–6 weeks. There were no clinical or laboratory factors identified that could predict relapse.

Mortality

Ten patients (14%) (6 females and 4 males) died of TTP. Two patients died just prior to starting plasma exchange, two died during the first procedure, two died after one TPE, and four patients died after 4, 5, 8, and 23 TPEs, respectively. The patient who died after eight TPEs, had had TTP 4 years earlier. During the last admission, he responded to plasma exchange by the fifth day, when his platelet count and LDH were normal. After three more TPEs, he insisted on going home. Three days later, he was readmitted in a comatose state with a platelet count of 12×10^9/L and LDH of 12,000 IU/L. He died before TPE could be started. The patient who died after 23 TPEs had a partial response following seven TPEs, with a platelet count of 122×10^9/L. The next day, she was taken for a splenectomy because of a poor response to TPEs. Post-splenectomy, her platelet count was 166×10^9/L but 3 days later, her platelet count dropped to 21×10^9/L from which it never increased. She died 15 days post-splenectomy. She had received daily one plasma volume TPE post-splenectomy, along with aspirin and dipyridamole throughout the treatment period. The remaining two patients who died after four and five TPEs had shown no response at all.

Early and Late Responders

Forty-nine patients out of 60 who had a complete response, could be evaluated for statistical analysis based on availability of daily platelet count and LDH values. They were grouped into early responders (ER) and late responders (LR) based on whether they required total of ≤ 9 or ≥ 10 TPEs for complete response. ER (n = 27) had a mean platelet count of 180×10^9/L (range: $79–317 \times 10^9$/L) by Day 5, mean LDH of 643 IU/L (range: 320–900 IU/L) by Day 7 and the mean total TPEs required were six (median 7, range 4–9). LR (n = 22) had a mean platelet count of 122×10^9/L (range: $33–264 \times 10^9$/L) on Day 5, mean LDH was 1,126 IU/L (range: 259–2,610 IU/L) on Day 7 and mean total TPEs required were 24 (median 19, range: 10–85). Platelet counts and serum LDH were compared in these two groups on Day 1, 3, 5, and 7. It was observed that platelet counts were significantly higher ($P = 0.01–0.03$) in the ER group on Days 1, 3, and 5 (Fig. 2). However, LDH values did not differ significantly on these days (Fig. 3). LR had normal mean platelet counts (154×10^9/L) on Day 7 but the mean LDH was still high (885 IU/L).

Exacerbation of TTP was seen in 17/22 (77%) LRs and in 2/27 (7%) ERs. Two patients had two episodes and one had three episodes of exacerbation in the LR group. The remainder all had one episode of exacerbation.

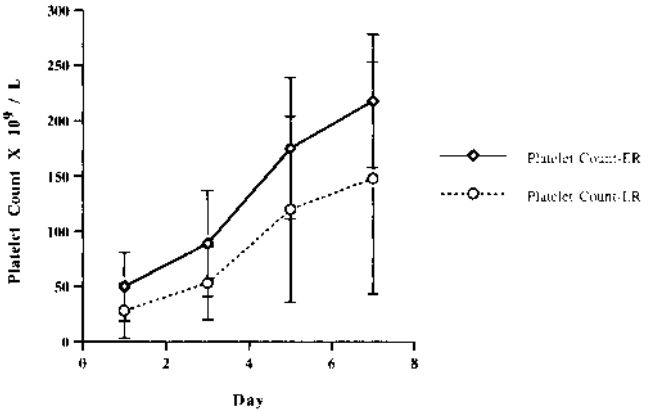

Fig. 2. Platelet counts of early and late responders (ER, LR) plotted for Days 1, 3, 5, and 7. Differences were significant on Days 1, 3, and 5 ($P < .01$, .03, .01, respectively).

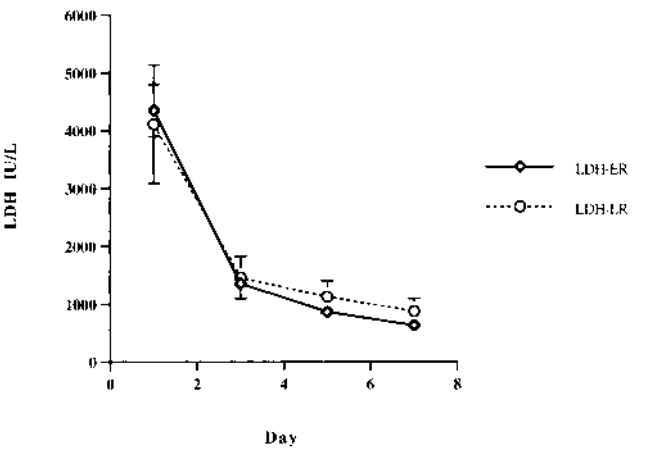

Fig. 3. Serum LDH values in international units/dl for early and later responders (ER, LR) plotted for Days 1, 3, 5, and 7. Only the LDH levels on Day 7 were significantly different ($P < .01$).

The majority of LRs were gradually weaned from their plasma exchanges, from daily to alternate and then twice a week before discontinuing. They were advised to continue taking antiplatelet drugs and to have more frequent physician follow-up. Patients with exacerbation in the ER group were treated no differently than the rest of the ERs. Four patients in LR (18%) and two (7%) in ER had relapse of the TTP ($P \geq 0.5$).

Outcome in Comatose Patients

Thirteen patients were in coma/semicoma at the time of presentation. Six patients died, two before plasma exchange, one during the procedure, two after one exchange, and one after five exchanges. The patient who died after five exchanges had received two TPEs of one plasma volume each on Day 1 followed by once a day TPE of one plasma volume. Seven patients responded to plasma exchange with complete neurological recovery. Five of these seven had received two TPEs of one plasma volume each on Day 1 followed by daily one volume TPE. There was no significant difference in the platelet count or LDH on Day 1 between the comatose patients who survived and those who did not (Table III). However, two TPEs on Day 1 in comatose patients was associated with a significant difference in survival ($P = 0.05$). Of these seven survivors, five were ERs and two were LRs. Both LRs had one exacerbation each. None of these seven survivors had relapse of the disease (minimum follow-up of 4 months).

TABLE III. Hematological Features in Died Vs. Responded

	Died	Responded	*P*
Hematocrit (%)	27 ± 6	24 ± 6	N.S.
Platelets ($\times 10^9$/L)	32 ± 28	40 ± 31	N.S.
LDH (IU/L)	5,707 ± 4,188	3,622 ± 2,840	N.S.

Transfusions

Packed red cells (1–8 U) were given to 21/70 (29%) patients for symptomatic severe anemia, the majority of the patients receiving 1–2 U. The patients who received packed red cells had good response to TPE and none of them died. For one patient who had severe anemia (Hct 18%) at the time of presentation, the Cobe Spectra machine was primed with 1 U of red cell mass. This patient had a complete response following 15 plasma exchanges. The apheresis machine was also primed with blood during each of five TPEs for an 8-year-old boy. He had an excellent response and was discharged home with mild renal insufficiency. Only 4/70 (6%) patients were given platelet transfusions for severe thrombocytopenia and all of them responded completely to plasma exchange.

Adjunct Therapy

Corticosteroids were given to 33 (47%), aspirin to 12 (20%), and dipyridamole to 9 (13%) patients, either alone or in combination. VCR was given to 5 patients in the LR group with exacerbations, at 2 mg/week for 2–6 weeks. One patient underwent splenectomy, but she died 15 days post-operatively.

Side Effects

Allergic reactions in the form of hives, pruritus, dyspnea, and shaking chills were observed in 26 (38%) cases. These patients were premedicated with diphenhydramine (50–100 mg) and acetaminophen (350 mg) before the start of each TPE and sometimes midway through the procedure. Some patients required administration of hydrocortisone (100 mg IV) for moderate to severe allergic reactions including shortness of breath and generalized urticaria. Some of the other patients were premedicated according to a particular hospital's transfusion policy.

DISCUSSION

The 85.7% complete response rate to plasma exchange with FFP in primary TTP patients in the present series reflects the dramatic reversal of the mortality rate since the advent of plasma therapy [3,14]. The response rate was 91% when we excluded four patients who died before they received at least one TPE. Plasma therapy in the form of daily exchanges of one or more plasma volumes appears to be superior to plasma infusions in TTP patients. A multicenter, national trial conducted by the Canadian Apheresis Study Group [15] found a higher failure and morality rate in TTP patients who were treated by plasma infusion alone compared to patients treated with plasma exchange with FFP. Those patients who responded to plasma infusion had a high relapse rate. Similar disappointingly high relapses have been reported by Bell et al. [14] in TTP patients who were receiving plasma infusion as a maintenance therapy.

The inadequate response to plasma infusion in patients with TTP could be due either to insufficient amount of plasma infused to replace a hypothetical deficiency or failure of plasma infusion to remove a substance(s) that are important in pathogenesis. The overall relapse rate in our series was 18%. None of our patients was treated with plasma infusions alone.

In the recent epidemiological study for the period 1968 to 1991 by Torok et al. [16], it was reported that the number of deaths nationally from TTP has been steadily increasing after decline in the initial 5 years of this study. The authors conclude that this increase in mortality can be largely accounted for by an increased incidence of reported cases of TTP over the period of time covered by the study. During the early years of the study, the incidence was estimated to be on the order of one case per million U.S. residents per year. This increased to 3.7 cases per million in the later years of this study. The latter estimate was made using the number of deaths attributed to TTP from national death statistics and an assumed 70% survival rate for the disease. Based on the present study, if the current survival rate of TTP treated in a community setting is closer to 85%, that would result in a further increase in the estimated incidence of TTP (an estimated 7.3 cases per million population annually). The present study with its reported 85% survival rate and the study by Torok noting that the mortality from TTP appears to be increasing in the population at large are not necessarily in conflict. The latter increased mortality is attributed largely to an increased incidence of reported cases and not to an increase in mortality *rate* for the disease.

There appeared to be two treatment response patterns in our series. Patients in one group responded quickly to TPEs with normalization of platelet count by Day 5 (mean 180×10^9/L), and correction of the LDH value by the seventh day (mean LDH 643 IU). They received a median of seven total TPEs, and were classified as "early responders"-ER. The other group designated "late responders" or LR had a definite increase in platelet counts by Day 5 (mean platelet count 122×10^9/L), mildly increased LDH by Day 7 (mean LDH 885), and required a median of 19 total TPEs. ERs had significantly higher platelet counts on Days 1, 3, and 5 ($P = 0.01$–0.03). The LDH values did not differ significantly between the two groups, except on Day 7.

The principle reason for prolonged therapy in the LR group was that 77% had exacerbation of their disease. In the ER group only 7% had exacerbation and these did not require more than nine total TPEs. The mean number of TPEs received by the ER group was six (median 7, range 4–9) as compared to 24 (median 19, range 10–85) TPEs for LR ($P = 0.001$). The relapse rate for TTP was higher (18%) in the LR group as compared to the ER group (7%) but this difference was not statistically significant.

Although the ER and LR groups could not be distinguished prospectively, in retrospect there were differences in the therapeutic approaches which were dictated by the day-to-day response to treatment. The ER group was generally given 2–3 more daily TPEs after the platelet count and LDH values became normal. Corticosteroids and antiplatelet drugs were gradually tapered off. The LR group, because of the high frequency of exacerbation, were gradually weaned from plasma exchange therapy, from daily one plasma volume exchanges to alternate day exchanges followed by twice a week exchanges.

Ten patients (14%) died of the disease. Of these, two died before starting TPEs, two died during and two after the first procedure. This suggests that the disease was fulminant when TPE was initiated. The patient who left against medical advise and died of TTP within 2 days, illustrates the importance of careful monitoring of clinical and laboratory parameters in the immediate post-TPE period for exacerbation of the disease. One patient who had shown initial response to TPEs, underwent splenectomy. However, the post-splenectomy course was very stormy and she died 15 days later despite receiving daily TPEs and anti-platelet drugs. This case resembles those described by Bell et al. [14] in which six splenectomized patients had a stormy course and one died. Our current practice is to recommend splenectomy only as a last resort because of the effectiveness of intensive plasma exchange therapy.

One patient, not included in this study, was initially thought to have primary TTP and achieved only partial response after 25 TPEs and ultimately had a fatal outcome. At autopsy it was found that she had a recurrence of colonic cancer (which had been treated by surgery and chemotherapy 6 years earlier) with widespread metastasis. Therefore, if a TTP patient does not show any response to daily plasma exchanges, a careful evaluation

for any underlying cause of secondary TTP should be considered. Secondary TTP cases usually do not respond well to TPEs [8,9].

Thirteen patients were in coma/semicoma at presentation. Six died, making this a bad prognostic indicator. Five of the seven survivors had received two plasma exchanges of one plasma volume each on Day 1. Aggressive early plasma exchange appears be a worthwhile strategy in patients with severe neurological symptoms. Five of these seven survivors belonged to the ER group and two to the LR group. None of the survivors in the ER group had exacerbation of disease whereas both the survivors in the LR group had one exacerbation each. None of these survivors had relapse of TTP.

In the LR group, four patients received VCR and TPE during the exacerbation of TTP with excellent results. Since these patients had previously shown complete response to TPE, it is difficult to attribute success to VCR alone. The literature reports that VCR therapy has been successful following the failure of FFP treatment [11,12]. Similarly, the contribution of corticosteroids and antiplatelet drugs in the final outcome of the treatment could not be assessed in our patients.

Conclusions

There was a complete response to plasma exchange therapy in 91% of the patients who had received at least one TPE. Patients with coma/semicoma belong to a high risk group with a higher mortality rate. Although there appeared to be two different response patterns to TPE with ERs having an excellent response with fewer exacerbations and relapses as compared to LRs, it is not possible to prospectively differentiate LRs from ERs at the outset of therapy. Therefore it is difficult to make recommendations about specific therapies based on this observation. Our approach to therapy in TTP has included an increase in the aggressiveness of treatment used (increased TPE volumes, prolongation of TPE therapy) in patients who fail to show a prompt return to normal of the laboratory parameters, in particular platelet count and LDH. Although not rigorously examined, this approach may contribute to the favorable survival rate we have observed in the TTP cases treated at our institution.

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